Review Article

Systematic Review of the Effects of Ultraviolet Radiation on Markers of Metabolic Dysfunction

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Abstract
Emerging findings suggest that exposure to ultraviolet wavelengths of sunlight modulates metabolic function. Here we review the metabolic effects of exposure to ultraviolet radiation (UVR), focusing on the effects of phototherapies (that administer UVR), and advice to increase sun exposure in individuals enrolled in clinical trials and intervention studies. We identified 25 studies in which the effects of UVR on metabolic outcomes were examined, including: narrowband ultraviolet B phototherapy (nbUVB, n = 12); psoralen ultraviolet A phototherapy (n = 4); other types of UVR phototherapy (n = 5); and sun exposure advice (n = 5). Most studies recruited a small number of participants (≤100), who were middle-aged individuals undergoing treatment for psoriasis flare, with phototherapy or sun exposure advice administered for ≤12 weeks. Data obtained at baseline were usually compared with an endpoint following treatment with UVR, for a limited number of outcomes. There were few studies in which markers of glucose metabolism were assessed, with some beneficial effects of sun exposure (but not phototherapy) reported. LDL-cholesterol levels were lower in individuals receiving sun exposure advice, while treatment with nbUVB reduced blood concentrations of inflammatory markers (C-reactive protein and interleukin-6). Future studies should focus on determining whether the effects of these interventions change with time, and if they are dependent on the source of UVR (i.e. phototherapy or sun exposure) and wavelength(s) of light administered. Furthermore, studies need to measure a variety of (clinical) markers of glucose metabolism, adiposity and inflammation, control for factors such as skin type and sex, and stratify participants for metabolic disease diagnosis.

Introduction

Ultraviolet radiation (UVR), like that found in sunlight, has many known effects on skin health, including harms such as sunburn and skin cancer and benefits like synthesis of vitamin D. UVR is often used clinically to effectively treat inflammatory skin conditions, such as psoriasis, delivered as narrowband ultraviolet B phototherapy (nbUVB) or psoralen with ultraviolet A phototherapy (pUVA). During nbUVB, participants are exposed to light of 311–313 nm in wavelength (λ), while for pUVA, photosensitising psoralen is administered prior to UVA irradiation (λ = 315–400 nm, UVA). The benefits of these phototherapies in reducing skin disease in dermatological settings are well established. However less is known of their potential to regulate co-morbidities that often accompany inflammatory skin diseases, such as the increased risk for obesity and metabolic disorders (e.g. type 2 diabetes[1]). It has been increasingly recognised that these disorders are often found in patients with severe chronic psoriasis. However the nature and the direction of the relationships between skin inflammation and metabolic dysfunction are not clear. Animal models suggest that the skin inflammation of psoriasis can be caused by obesity, while chronic low-grade inflammation of psoriasis may cause metabolic dysfunction.[2,3] Chronic inflammation[4,5] and oxidative stress[1] are intrinsically linked with the development of insulin resistance and type 2 diabetes, potentially through reciprocal actions of pro-inflammatory cytokines (e.g. tumour necrosis factor (TNF)) that induce systemic (and dermal) inflammation during psoriasis (and metabolic dysfunction).[3]

Phototherapies are thought to improve skin health by inhibiting proliferation and inducing apoptosis of keratinocytes, and by inducing regulatory immune cells that suppress the pro-inflammatory responses that underpin skin conditions like psoriasis.[6] Indeed, exposure to UVB radiation (λ = 280–315 nm, UVB) has systemic anti-inflammatory effects.[7] Other reports suggest that nbUVB therapy modifies the skin microbiome with these changes linked to the capacity of this therapy to control psoriatic flare.[8] In addition, pre-clinical[9-11] and human studies[12-14] indicate that UVR may be beneficial for metabolic health. Adult mice fed a high fat diet and exposed repeatedly to sub-erythemal (non-burning) UVB (1 kJ/m^2) over 12 weeks gained less weight, exhibited reduced metabolic dysfunction (e.g. lower blood glucose during a glucose tolerance test), and less hepatic steatosis and inflammation compared to mock-treated mice.[10,11] Exposure to UVB also suppressed further weight gain and metabolic dysfunction in already 'overweight' mice,[9] suggesting that UVB may be effective when disease processes are already underway. Exposure to UVB induces dermal synthesis of the hormone-mediator, vitamin D. However, metabolically beneficial effects of UVB were independent of circulating 25-hydroxyvitamin D, with dietary vitamin D of limited benefit.[10] Similar vitamin D-independent pathways have been identified for UVB in suppressing skin inflammation.[15] Furthermore, while observational studies link vitamin D deficiency to increased risk of metabolic diseases such as obesity, type 2 diabetes and polycystic ovary syndrome, only limited benefits for vitamin D supplementation in preventing or treating these disorders have been described.[16] The metabolically beneficial effects of UVB have instead been linked to the release of nitric oxide from skin[10] with important anti-inflammatory effects also hypothesised for this pathway.[17]

Recently published narrative reviews have described the potential for UVR (delivered as a phototherapy or through sun exposure advice) to modulate metabolic dysfunction in other pre-clinical and human clinical and epidemiological settings,[12-14] focusing on mediators through which UVR could act (i.e. through vitamin D-dependent and/or -independent pathways).[12,13] In a review published by the Medical Board of the National Psoriasis Foundation, beneficial effects of common therapies of psoriasis, including phototherapy, were found on markers of cardiovascular risk and systemic inflammation. The authors called for more systematic reviews in this area.[18] In addition, accumulating evidence from pre-clinical[9-11] and human epidemiological studies[12-14] of the potential metabolic benefits of UVR suggest that a systematic review of its effects in clinical settings is warranted. Here we undertook a systematic review of published studies detailing the effects of UVR on clinical measures and biomarkers of adiposity and metabolic dysfunction in clinical trials and intervention studies, concentrating on the effects of phototherapies (that incorporate UVR) and specific advice to increase sun exposure.

Methodology and Article Identification

We searched for full-text articles with phototherapy and sun exposure, and adiposity and metabolic keywords within PubMed (1 January 1950 until 28 February 2019), using search terms described below, combining each 'UVR' keyword with each 'metabolic' keyword:

- *'UVR' keyword*: narrowband ultraviolet, pUVA, sun exposure, heliotherapy, phototherapy;

AND

- *'Metabolic' keyword*: metabolic, glucose, adipokine, cholesterol, body weight, BMI, adiposity, waist circumference, triglyceride, insulin.

These searches resulted in the identification of 5040 records, with a further 16 previously known. The primary author performed the data extraction and screening (**Figure 1** for PRISMA flow diagram for the identification of papers). Abstracts were screened to identify studies reporting human data that were original publications (and not reviews or duplicates) and written in English. This resulted in the identification of 400 articles, of which the full-text was screened, with 375 papers excluded (see Figure 1).

Studies were excluded if they:

1. did not report the effects of a phototherapy or sun exposure intervention (e.g. were population health-based association studies or pre-clinical studies);
2. did not report any effects of treatments on adiposity or metabolic-related outcomes, or showed insufficient data (e.g. baseline data not shown);
3. combined the results of non-phototherapy/non-sun exposure treatments with phototherapy/sun exposure treatments; or,
4. were duplicates or case reports.

Twenty-five peer-reviewed and full-text articles were identified for quantitative assessment, which were further divided into studies which characterised the effects of nbUVB (n = 12), pUVA (n = 4), treatment with UVA and/or UVB (other UVR, n = 5) and sun exposure advice (n = 5). **Table 1** provides an overview of the identified studies, including UVR intervention types, clinical study designs, any major consistent findings and limitations.

Narrowband Ultraviolet B Phototherapy

General Characteristics

We identified 12 research articles describing 10 clinical

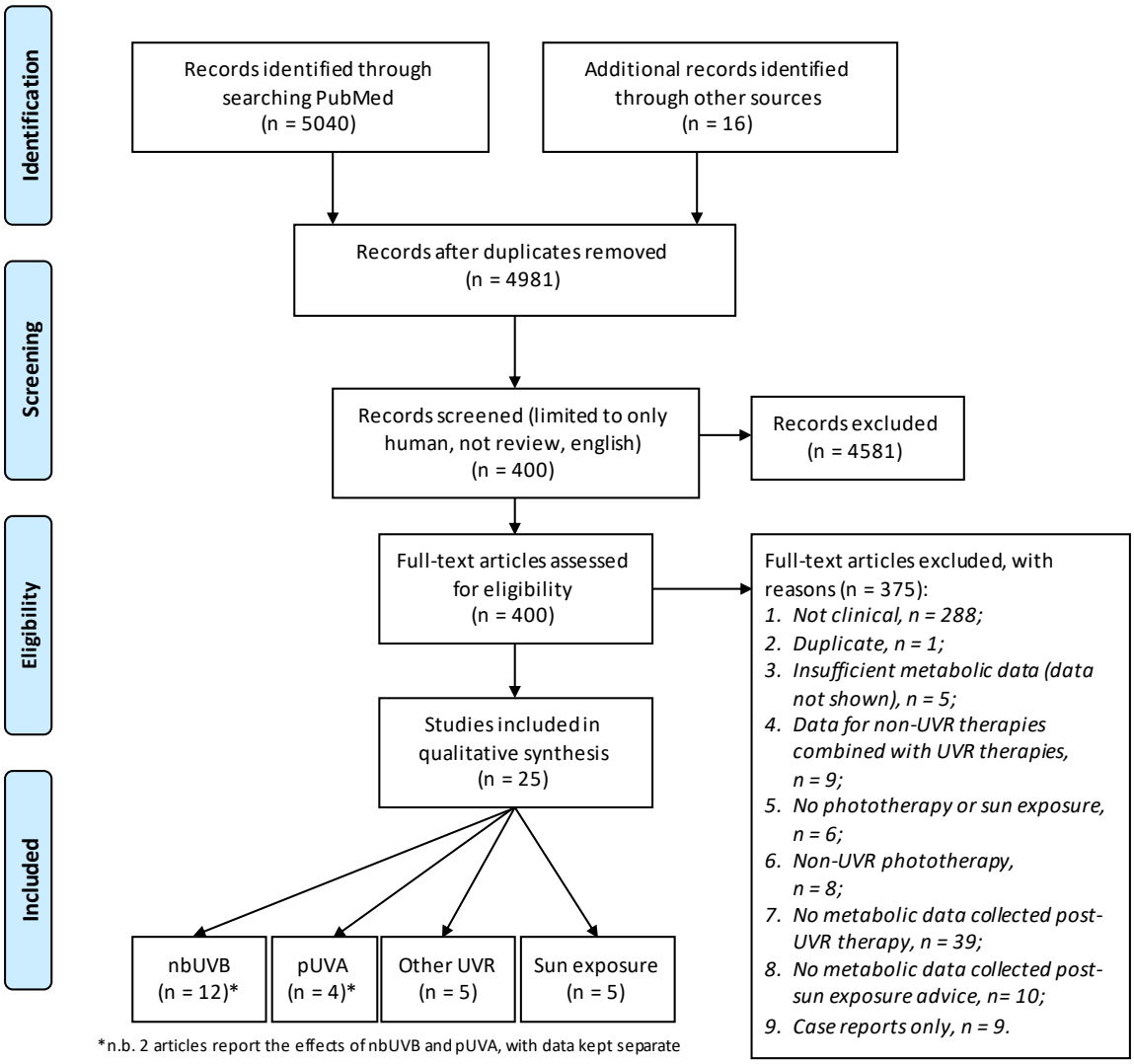

Figure 1. Flow diagram of articles identified for inclusion in this review.
nbUVB = narrowband ultraviolet B therapy; pUVA = psoralen with ultraviolet A therapy; UVR = ultraviolet radiation

intervention studies examining the effects of nbUVB on markers of adiposity, metabolic dysfunction and other outcomes (**Table 2**). Most studies were done in patients with psoriasis (9/10) and were of ≥12 weeks duration (5/10), although the length of treatment was not always clearly stated. The studies were fairly small in participant number (n = 10–58 for those receiving nbUVB), with mean age of participants of >35 years, with many (7/10) reporting findings collected from both men and women, although no study examined outcomes separately by sex. Nearly all studies were done in populations with mean/median body mass index (BMI) >25 kg/m^2 (indicative of overweight/obesity), except for Rui *et al.*, who differentiated outcomes by presence or absence of metabolic syndrome (MetS), such that those without MetS reported mean BMI <25 kg/m^2.[19] Skin type was reported in 4 of the 10 studies, with some variability in Fitzpatrick skin type between reports (Table 2). In 5 of the 10 studies, findings were reported for data collected following the final treatment compared to that collected prior to treatment (at baseline).

Effects of nbUVB on Adiposity Measures

In three studies, body weight was not affected by up to six months of treatment with nbUVB.[20-22] Similarly, in four studies, BMI was not significantly modulated by nbUVB[22-25] including one small study (n = 13 in nbUVB arm) of 24 weeks duration.[25] Other markers of adiposity, including waist circumference[20,23] and body fat,[23] were not affected by nbUVB.

Effects of nbUVB on Blood Cholesterols and Triglyceride

Plasma cholesterol levels (including total, low density lipoprotein (LDL) and high density lipoprotein (HDL))

Table 1. Summary of intervention studies reporting the effects of ultraviolet radiation on adiposity and markers of metabolic dysfunction.

Intervention	Clinical study type	Consistent effects reported for UVR Intervention			Limitations
		Adiposity outcomes	Metabolic outcomes	Other outcomes	
Nb-UVB (n=4)* [19,21,24,26]	Single-arm, in individuals with psoriasis (or other skin condition), BMI>25	No change in body weight or BMI	Small non-significant increases in blood LDL-cholesterol observed (comparing endpoint with baseline)	PASI, and blood PTH, CRP and IL-6 reduced Blood 25(OH)D increased	No placebo or control group for some studies Significant variability in length of treatment (2 weeks–6 months) Short treatment length (≤6 weeks) or length not stated (n=5) Participant number small (n<60 receiving nb-UVB) Limited data on markers of glucose metabolism Lack of specific reporting of some data or units of measurement
Nb-UVB (n=6) [20,22,23,25,27-29,47]	Clinical trials with control groups, in individuals with psoriasis, BMI>25				
pUVA (n=4) [26,27,30,31]	Mainly single-arm, in individuals with psoriasis (or other skin condition), BMI>25		No change in blood cholesterols	PASI reduced	No placebo or control group in most studies Participant number small (n<50 receiving pUVA) Limited data on adiposity and markers of glucose metabolism (with inconsistency in markers measured)
Other UVR (n=5) [32-36]	Mainly single-arm, in 'healthy' individuals, BMI>25 (or not stated)		Limited effects on blood cholesterols No change in blood glucose or insulin	Treatments with UVB increased blood 25(OH)D	No placebo or control group in most studies Significant variation in wavelengths, doses, and length (2–12 weeks) of UVR intervention Treatment length not always stated Participant number small (n≤61 receiving UVR) Limited data on metabolic markers
Sun exposure (n=5) [37-41]	Mainly single-arm, BMI>25 (or not stated)	No change in BMI	Reduction in blood LDL-cholesterol in some studies	Blood 25(OH)D increased	No placebo or control group in most studies Significant variation in recommended time in sun (20 min–6 h), length of study (7 days–12 months), and participant health status In most, participant number was small (n<60 receiving sun exposure advice) Sun exposure advice sometimes combined with other lifestyle advice Sun exposure levels not often measured

25-hydroxyvitamin D (25(OH)D); body mass index (BMI); C-reactive protein (CRP); interleukin-6 (IL-6); low density lipoprotein (LDL); narrowband ultraviolet B light therapy (nbUVB); psoralen ultraviolet A light therapy (pUVA); parathyroid hormone (PTH); psoriasis area severity index (PASI); ultraviolet radiation (UVR); ultraviolet A/B radiation (UVA/B)

*n = number of clinical studies

and/or triglyceride were examined in five studies, with nearly all reporting no significant effects of nbUVB[22,23,26,27] when comparing blood measured at the endpoint with baseline. Mehta *et al.* reported increased HDL-cholesterol in participants receiving nbUVB compared to a placebo group.[28] All studies reported small (but non-significant) increases in LDL-cholesterol with nbUVB therapy (comparing endpoint with baseline).[22,23,26-28]

Effects of nbUVB on Markers of Glucose Metabolism

In the few studies (3/10, Table 2) that investigated markers of glucose metabolism, there were no significant effects of nbUVB reported on homeostatic model assessment of insulin resistance (HOMA-IR),[23] glycated haemoglobin (HbA_{1c})[26] or circulating insulin[28] levels.

Effects of nbUVB on Adipokines

Four papers reported on concentrations of resistin,[20,23,25] adiponectin[25,28] and/or leptin[23,25,28] measured in blood (Table 2). Only one study reported significant changes after nbUVB, in which reduced leptin and resistin, and increased adiponectin levels, were observed after 24 weeks of therapy.[25] In the same study, psoriasis area severity index (PASI) scores were significantly reduced at an earlier timepoint (12 weeks),[25] with the other three studies shorter in duration (≤12 weeks).

Effects of nbUVB on Other Measures

PASI scores (in individuals with psoriasis) were reduced by nbUVB in the eight studies for which they were reported (Table 2). As expected, blood levels of 25-hydroxyvitamin D were increased,[22,23,26] and parathyroid hormone (PTH) levels were reduced[22,23] by nbUVB. In three of four studies, blood concentrations of C-reactive protein (CRP), a marker of acute inflammation, were reduced following treatment with nbUVB,[23,27,28] with no difference reported in the fourth study, which was much shorter in therapy duration (2 weeks),[26] compared to the other three (of 8–12 weeks in length). Interleukin-6 (IL-6) was measured in four studies, with one reporting no effect[20] and others reporting reduced concentrations in blood[19,28,29] after nbUVB. Other less frequently measured markers of inflammation that were reduced in blood following nbUVB included ferritin,[23] interleukins IL-8,[20] IL-17,[19] IL-22,[20] and TNF[19] (although TNF was not reduced in Mehta *et al.*[28]).

Are Meta-Analyses Examining the Effects of nbUVB on Some Outcomes Possible?

While the effects of nbUVB upon body weight, BMI, and circulating levels of CRP and IL-6 were reported in multiple studies (n ≥3), there was significant variability in the length of time of nbUVB treatment (e.g. 6–24 weeks for BMI)[23-25] with treatment length not clearly stated by all studies (e.g. not stated in two of three studies for IL-6).[19,20] Other issues included a lack of specific reporting of data for some outcomes (with data not reported in two of three studies for body weight,[20,22] and in one of four studies for IL-6[20]), or units of measurement (e.g. for CRP in one of three studies,[28] for IL-6 in one of four studies[19]) or reported as log-adjusted data (in one of four studies for IL-6[28]). LDL-cholesterol levels (mean/median, with units of measurement) were reported in four of five studies, of which three[22,23,27] examined the effects of nbUVB for ≥8 weeks (estimated for Romani *et al.*[23]); however, with data depicted as change between baseline and endpoint,[22] or as mean ± SD,[23] or median (interquartile ratio),[27] more information is required before a meta-analysis of the effect of nbUVB on LDL-cholesterol can be performed (e.g. whether data are normally distributed). In these studies, LDL-cholesterol levels were increased between baseline and the endpoint by 1.4,[22] 1.3[23] and 14.0[27] mg/dL (after comparing mean or median values for Romani *et al.*[23] and Coimbra *et al.*[27]). At this stage, further information is required before meta-analyses can be conducted.

Psoralen Ultraviolet A Phototherapy

We identified four research articles describing the effects of pUVA on adiposity, markers of metabolic dysfunction and other outcomes (**Table 3**). Three studies were undertaken in patients with psoriasis treated with pUVA for ≥12 weeks,[27,30,31] while the fourth was done in individuals with different skin conditions, who were treated with pUVA for only two weeks.[26] Participant numbers were small (n = 10–45), mean age was ~50 years, and most studies reported a mean BMI >25 kg/m^2. Skin type was reported in only one study (these were mostly individuals with Fitzpatrick skin types II-III).[26] Most findings were reported for data collected following the final treatment compared to that collected at baseline. Only one study examined the effects of pUVA on BMI and abdominal obesity (waist-to-hip ratio), with no effect observed after 24 weeks of treatment.[30] Total cholesterol levels were measured in three studies, and these were not affected by 2–24 weeks of pUVA. There were no significant effects on blood concentrations of HDL-cholesterol, LDL-cholesterol, triglyceride or apolipoproteins-A/B,[26,27,30,31] although after 12 weeks of pUVA, lipoprotein(a) levels in blood were significantly reduced in one study.[27] Treatment with pUVA did not affect fasting blood glucose or insulin levels, HOMA-IR or QUICKI scores after 24 weeks,[30] or HbA_{1c} levels after two weeks[26] of therapy. In one study, increased adiponectin levels were observed in blood after 12 weeks of pUVA.[27] Reduced PASI scores were observed in the two studies in which it was measured in individuals with psoriasis undergoing pUVA.[27,30] Circulating levels of CRP were reduced by pUVA treatment in one study[27] but not in two other studies.[26,30]

Table 2. Intervention studies reporting the effects of nbUVB on adiposity and markers of metabolic dysfunction.

Publication Location	Treatment, dose and length	Population and skin type^	Effects of nbUVB on adiposity outcomes*	Effects of nbUVB on metabolic outcomes*	Effects of nbUVB on other outcomes*
Johnston *et al.* 2008[20] Iceland	nbUVB (dose not stated) with bathing in lagoon; or Control group Length: not stated	N = 30 (nbUVB, 14F:16M, mean BMI = 30.5) Chronic plaque psoriasis N = 29 (matched controls) Adults (mean = 53 y) Skin type not reported	No change in body weight or waist circumference	No change in resistin	Reduced PASI score, interleukin-8 and interleukin-22 No change in interleukin-1ß or IL-6
Coimbra *et al.* 2010[27] Portugal	nbUVB (3x/week; total dose not stated); or Control group Length: 12 weeks	N = 11 (nbUVB, sex ratio not stated, median BMI = 27.5) Adults (mean = 43 y) Psoriasis vulgaris N = 37 ('healthy' controls) Skin type not reported	†	No change in cholesterol (HDL-, LDL-, total), triglyceride, oxidised-LDL-cholesterol No change in apolipoprotein A/B, lipoprotein(a), 'total antioxidant status'	Reduced PASI score and CRP
Kimball *et al.* 2012[21] USA	nbUVB (3x/week, total dose not stated) Length: 12 weeks	N = 10 (nbUVB, 5F:5M, BMI>25) Adults (mean = 48 y) Chronic moderate-severe psoriasis Skin type not reported	No change in body weight		Reduced PASI score
Magina *et al.* 2012[24] Portugal	nbUVB (3x/week, 21.8 J/cm^2 mean total dose) Length: 6 weeks	N = 20 (nbUVB, 9F:11M, mean BMI = 26.4) Adults (mean = 50 y) Chronic plaque psoriasis with no flare for ≥12 weeks Skin type = type II-III	No change in BMI		Reduced PASI and DLQI scores
Romani *et al.* 2012, 2013a, 2013b[23,29,47] Spain	nbUVB (2-3x/week; 25 J/cm^2 mean total dose); or Control (matched) Length: not stated**	N = 50 (nbUVB, 19F:31M, mean BMI = 27.6) N = 50 (controls) Adults (mean = 46 y) Moderate-severe psoriasis Skin type = mostly type III	No change in body fat (%), BMI, or waist circumference	No change in HOMA-IR, leptin, resistin, HDL- or LDL-cholesterol, triglycerides, apolipoprotein-B, or metabolic syndrome (MetS) prevalence	Reduced PASI score, DLQI score, CRP, IL-6, ferritin, PTH, vitamin B_{12} Increased 25(OH)D, vitamin B_6 No change in LPS-binding protein, retinol-binding protein, lipocalin-2, soluble tumour necrosis receptor-1
Takahashi *et al.* 2013[25] Japan	nbUVB (total dose not stated); or Biologic (infliximab, adalimumab, ustekinumab) Length: 24 weeks	N = 13 (nbUVB, sex ratio not stated, mean BMI = 26.4) N = 17 (biologic) Adults (mean = 46 y) Plaque-type psoriasis Skin type not reported	No change in BMI	Increased adiponectin Reduced leptin, resistin	Reduced PASI score

Publication Location	Treatment, dose and length	Population and skin type^	Effects of nbUVB on adiposity outcomes*	Effects of nbUVB on metabolic outcomes*	Effects of nbUVB on other outcomes*
Weinhold *et al.* 2016[26] Germany	nbUVB (5x/week; mean total dose = 1.9 J/cm^2) Length: 2 weeks	N = 22 (nbUVB, sex ratio not stated, mean BMI = 27.0) Adults (mean = 49 y) Different skin diseases (including psoriasis, atopic dermatitis) Skin type = 63% type I-III		No change in HbA_{1c}, triglyceride, cholesterol (HDL-, LDL-, total)	Increased 25(OH)D No change in CRP No change in resting blood pressure
Ponda *et al.* 2017[22] USA	nbUVB (2x/week, total dose not stated); or Vitamin D_3 (50,000 IU/ week) Length: 2-6 months	N = 58 (nbUVB, 33F:25M, mean BMI = 29.4) N = 60 (vitamin D) Adults (mean = 39 y) With vitamin D-deficiency Skin type = 90% type III-VI	No change in body weight or BMI	No change in cholesterol (HDL-, LDL-, total)	Increased 25(OH)D No change in calcium or phosphorus Reduced PTH
Rui *et al.* 2017[19] China	nbUVB (10 sessions) Length: not specified	N = 55 (nbUVB, 28F:37M, mean BMI = 27.3 or 22.6 with or without MetS, respectively) Adults (mean ~39 y) Psoriasis vulgaris, excluding psoriatic arthritis Skin type not reported		Effects of nbUVB on circulating inflammatory mediators reduced in those with MetS	Reduced PASI score, IL-6, IL-17, TNF (dependent on presence on MetS)
Mehta *et al.* 2018[28] USA	nbUVB (3x/week, total dose not stated); or TNF inhibitor (adalimumab), or, Placebo Length: 12 weeks	N = 33 (nbUVB, 10F:23M, mean BMI = 32.6) N = 33 (adalimumab) N = 31 (placebo) Adults (mean = 42 y) Chronic moderate-severe psoriasis Skin type not reported		Increased HDL-cholesterol (compared to placebo) No change in vascular inflammation, cholesterol efflux, triglyceride, insulin, adiponectin, leptin (compared to placebo)	Reduced CRP, IL-6 (compared to placebo) No change in TNF or GlycA (compared to placebo)

^Skin type refers to the Fitzpatrick system for scoring skin type from type I (lightest skin, most susceptible to burn with sun exposure) to type VI (darkest skin, least susceptible to burn with sun exposure). *Aside from PASI/DLQR scores, adiposity/metabolic outcomes/disease prevalence, data refers to metabolites and proteins measured in blood; unless otherwise stated data compares baseline with study end. **Participants asked not to change lifestyle, sun exposure was recorded but not reported. †Blank fields mean these parameters were not measured in the study rather than there were no significant findings.
25-hydroxyvitamin D (25(OH)D); body mass index (BMI); C-reactive protein (CRP); dermatology life quality index (DLQI); female:male ratio (F:M); glycoprotein acetyls (GlycA); glycated haemoglobin (HbA_{1c}); high density lipoprotein (HDL); homeostatic model assessment of insulin resistance (HOMA-IR); interleukin-6 (IL-6); interleukin-17 (IL-17); low density lipoprotein (LDL); metabolic syndrome (MetS); narrowband ultraviolet B light therapy (nbUVB); parathyroid hormone (PTH); psoriasis area severity index (PASI); tumour necrosis factor (TNF)

Table 3. Intervention studies reporting the effects of pUVA on adiposity and markers of metabolic dysfunction.

Publication Location	Treatment, dose and length	Population and skin type^	Effects of pUVA on adiposity outcomes*	Effects of pUVA on metabolic outcomes*	Effects of pUVA on other outcomes*
Lawrence *et al.* 1984[31] United Kingdom	pUVA (+ placebo) (3x/week; mean total dose = 113.1 J/cm^2); or Etretinate (a retinoid) then pUVA Length: 18 weeks (after 2 weeks of placebo/etritinate alone)	N = 10 (pUVA, 9F: 1M, median BMI = not stated) N = 10 (pUVA + etretinate) Adults (mean = 52 y) Palmoplantar pustular psoriasis or hyperkeratotic psoriasis of palms and soles Skin type not reported	†	No change in fasting triglyceride	No change in fasting aspartate aminotransferase, γ-glutamyl transferase, bilirubin, urea, electrolytes, blood count
Coimbra *et al.* 2010[27] Portugal	pUVA (3x/week; total dose not stated); or Control group Length: 12 weeks	N = 13 (pUVA, sex ratio not stated, median BMI = 27.5) Adults (mean = 43 y) Psoriasis vulgaris N = 37 ('healthy controls) Skin type not reported		Increased adiponectin Reduced lipoprotein(a) Non-significant increase in apolipoprotein B Non-significant decrease in oxidised LDL-cholesterol No change in cholesterol (HDL-, LDL-, total), apolipoprotein-A	Reduced PASI scores Reduced 'total antioxidant status' and CRP
Campanati *et al.* 2013[30] Italy	pUVA (2x/week, total dose not stated); or TNF inhibitor (etanercept) Length: 24 weeks	N = 45 (pUVA, sex ratio not stated, median BMI = 28.0) N = 44 (etanercept) Adults (mean = 53 y) Moderate-severe psoriasis Skin type not reported	No effect on BMI, abdominal obesity (waist:hip ratio)	No change in fasting blood glucose, insulin, HOMA-IR, QUICKI, triglycerides, total cholesterol	Reduced PASI score No change in aspartate aminotransferase, alanine aminotransferase, CRP, liver ultrasound fibrosis score
Weinhold *et al.* 2016[26] Germany	pUVA (5x/week, mean total dose = 6.9 J/cm^2) Length: 2 weeks	N = 11 (pUVA, sex ratio not stated, mean BMI = 27.0) Adults (mean = 49 y) Different skin diseases (inc. psoriasis, atopic dermatitis) Skin type = 63% type I-III		No change in HbA_{1c}, cholesterol (HDL-, LDL-, total), triglyceride	No change in 25(OH)D or CRP Reduced resting systolic blood pressure

^Skin type refers to the Fitzpatrick system for scoring skin type from type I (lightest skin, most susceptible to burn with sun exposure) to type VI (darkest skin, least susceptible to burn with sun exposure). *Aside from PASI scores, adiposity/metabolic outcomes/disease prevalence, data refers to metabolites and proteins measured in blood; unless otherwise stated data compares baseline with study end. †Blank fields mean these parameters were not measured in the study rather than there were no significant findings.

25-hydroxyvitamin D (25(OH)D); body mass index (BMI); C-reactive protein (CRP); glycated haemoglobin (HbA_{1c}); high density lipoprotein (HDL); homeostatic model assessment of insulin resistance (HOMA-IR); low density lipoprotein (LDL); psoriasis area severity index (PASI); psoralen ultraviolet A light therapy (pUVA); quantitative insulin sensitivity check index (QUICKI)

Other UVR Phototherapies

Five studies were identified in which treatments with UVA and/or UVB were administered for varying lengths of time (between 1 and 12 weeks) and doses (both erythemal and suberythemal were tested) to mainly 'healthy' populations of adults[32-35] (except for those who were individuals with psoriasis[36]) (**Table 4**). In three studies, mean BMI was ≥25 kg/m^2,[33-35] with BMI not reported in the other papers.[32,36] Skin type was reported in three (of the five) studies, two of which reported findings from individuals who were mainly Fitzpatrick skin types II-III. In Scragg *et al.*, there was no significant effect of either UVA or UVB, administered repeatedly over 12 weeks, on body weight, BMI, or cholesterol levels observed in vitamin D-deficient adults comparing baseline with the endpoint 12 weeks later.[34] Carbone *et al.* similarly reported no effects of broad-spectrum UVR (UVA+UVB) on blood cholesterols of healthy adults.[33] However, in their 'control' group, increased LDL-cholesterol levels were observed in individuals exposed to a 'UVB with UVA-attenuated' phototherapy (comparing baseline with 12 weeks).[33] Both phototherapies in that study reduced blood levels of apolipoprotein A-I and lipoprotein(a).[33] No changes in fasting glucose or insulin were observed after treatment of healthy adults for two weeks with UVB[32] or vitamin D-deficient adults with UVA or UVB for 12 weeks.[34] However, glucagon-induced insulin secretion was increased two days after healthy adults were exposed to UVB.[32] Reduced levels of resistin but not leptin were observed in a study done in participants with psoriasis, in which the results of nbUVB (n = 5) and pUVA (n = 31) therapy were combined.[36] Finally, in healthy young adults, reduced oxygen utilisation and metabolic rate were observed along with increases in blood nitrite, immediately (early, short-term, ≤30 min) after exposure to UVA.[35]

Sun Exposure

Five intervention studies were identified in which participants were given advice to increase their sun exposure (**Table 5**). The studies varied considerably in: the duration of the intervention (from 7 days to 12 months); the recommended daily time in the sun (from 20 min to 6 h); and the participant health status ('healthy', overweight/obese, with psoriasis).[37-41] Sun exposure advice was sometimes combined with advice to increase dietary vitamin D intake[38] or reduce caloric intake/increase physical activity,[39] making it difficult to determine the specific effects of sun exposure. In one study, sun exposure levels were found to be increased by advice to increase sun exposure (by going for a walk outdoors for 20 min between 11 am and 3 pm) as measured via questionnaire.[41] Mean BMI was >25 kg/m^2 in all studies, except for one in which it was not reported.[40] Skin type was reported in only two studies,[37,40] where individuals were mainly Fitzpatrick skin types II-III. In three studies, there were no effects on BMI of sun exposure administered as part of 'climate therapy'[37] (see Table 5 for further information on this intervention) with dietary vitamin D advice[38] or lifestyle modification.[39] Beneficial effects of advice to increase sun exposure on blood LDL-cholesterol and triglyceride levels were reported in two studies,[39,41] but levels were not changed with the intervention in others.[37,38] One study reported reduced prevalence of individuals with high triglyceride levels (>1.7 mmol/L) after 12 months with sun exposure advice.[38] Conversely, increased HDL-cholesterol levels were observed in individuals given advice to increase sun exposure in two studies.[37,38] While no significant effects of sun exposure on blood glucose were observed,[37,38,40] reduced HbA_{1c} levels were observed in one study,[37] and blood glucose levels may have been 'normalised' in individuals with pre-diabetes in the sun exposure advice study arm of another study.[39]

Discussion

Here, we have systematically reviewed the effects of UVR administered as part of phototherapy or through sun exposure advice on markers of metabolic dysfunction and adiposity in intervention studies. Most identified studies had small sample sizes (≤100 participants), were short in duration (≤12 weeks for 13/20 studies in which study length was reported), involved older adults (>35 years-of-age), and compared pre- and post-intervention levels of a limited number of measures. Overall, few studies assessed markers of glucose metabolism; beneficial effects of sun exposure advice were seen in some,[37,39] but not all,[38,40] studies. Measures of adiposity, including BMI and waist/hip circumference, were not significantly modified by UVR phototherapy/sun exposure advice. It may be that longer times (than used in the identified studies) are needed for significant effects on adiposity to be observed. Furthermore, more studies using 'gold-standard' means of determining adiposity (e.g. dual-energy X-ray absorptiometry) are needed to determine if there are effects on specific deposits of adipose tissue (e.g. subcutaneous vs. visceral). Surprisingly, in five studies, small and statistically non-significant increases in LDL-cholesterol levels were observed after treatment with nbUVB,[22,23,26-28] and significantly increased LDL-cholesterol levels were observed in healthy adults exposed to a 'UVB with UVA-attenuated' phototherapy intervention.[33] Interestingly, reduced LDL-cholesterol concentrations in blood were observed in individuals given advice to spend more time in the sun over a period of six months[39,41] - an effect in the opposite direction to that of nbUVB. In three of four studies, nbUVB reduced blood markers of systemic inflammation, with reductions in CRP[23,27,28] and IL-6[19,28,29] observed following treatment, as also identified previously.[18] These findings point towards potential significant effects of UVR on markers of systemic inflammation with less certainty of its effects on metabolic function.

Table 4. Effects of UVA and/or UVB radiation on adiposity and markers of metabolic dysfunction in clinical studies.

Publication Location	Treatment, dose and length	Population and skin type^	Effects of UVR on adiposity outcomes*	Effects of UVR on metabolic outcomes*	Effects of UVR on other outcomes*
Colas *et al.* 1989[32] France	UVB (2x/week, 1xMED/ exposure, total dose not stated) Length: 2 weeks	N = 6 (UVB, 2M:4F, BMI not stated) Adults (age range = 19-37 y) Healthy Skin type not reported	†	No change in fasting glucose or insulin Increased cumulative insulin above basal levels, and peak insulin (measuring during glucagon challenge), comparing baseline with 2 days post-UVR	Increased 25(OH)D
Carbone *et al*. 2008[33] USA	UVA+UVB; or UVB with UVA-attenuated ('control') (2x/week, sub-erythemal by skin type, total dose not stated) Length: 12 weeks	N = 27 (UVA+UVB, 15F:12M; mean BMI = 26.5) N = 24 (UVB with UVA attenuated = 'control', 15F:9M; mean BMI = 27.4) Adults (mean ~31 y) Healthy Skin type = 67% type II-III		No change in cholesterol (total, LDL-, HDL-), triglycerides, apolipoprotein A-II Reduced apolipoprotein A-I and lipoprotein(a) in both treatments Increased cholesterol (total, LDL-) and apolipoprotein A-II in 'control'	Increased 25(OH)D
Scragg *et al.* 2011[34] New Zealand	UVB or UVA (24 whole body exposures; total dose not stated) Length: 12 weeks	N = 61 (UVA; 43F:18M; mean BMI = 34.1) N = 58 (UVB; 44F:14M; mean BMI = 33.2) Adults (mean ~57 y) With vitamin D deficiency (25(OH)D <50 nmol/L) Skin type = mixed types I-VI	No change in body weight, BMI	No change in fasting glucose, insulin, insulin sensitivity index or cholesterol (total, LDL-, HDL-) with either treatment	Increased 25(OH)D for both treatments No change in calcium, PTH or blood pressure with either treatment
Kawashima *et al*. 2011[36] Japan	nbUVB (3x/week, 15 J/cm^2 total dose); or bath pUVA (46 J/cm^2 total) Length: not stated	Data combined for N = 5 (nbUVB) and N = 31 (pUVA) (6F:30M) mean BMI not stated) Adults (mean = 55 y) Psoriasis vulgaris or pustular psoriasis Skin type not reported		Reduced resistin No change in leptin	Reduced PASI scores
Monaghan *et al*. 2018[35] Scotland	UVA (0, 10 or 20 J/cm^2) Length: 2 treatments, 7 days apart with baseline compared to ≤30 min post-exposure	N = 10 (UVA, 0F:10M, mean BMI ~25) Adults (mean = 28 y) Healthy Skin type = all type II-III		Reduced whole body oxygen utilisation and resting metabolic rate with 10 or 20 J/cm^2 UVA (although not significant with 20 J/cm^2 UVA)	Increased nitrite immediately (but not 30 min) after 20 J/ cm^2 UVA No change in blood pressure with either dose of UVA

^Skin type refers to the Fitzpatrick system for scoring skin type from type I (lightest skin, most susceptible to burn with sun exposure) to type VI (darkest skin, least susceptible to burn with sun exposure). *Aside from PASI scores, adiposity/metabolic outcomes/disease prevalence, data refers to metabolites and proteins measured in blood; unless otherwise stated data compares baseline with study end. †Blank fields mean these parameters were not measured in the study rather than there were no significant findings.

25-hydroxyvitamin D (25(OH)D); body mass index (BMI); C-reactive protein (CRP); female:male ratio (F:M); high density lipoprotein (HDL); homeostatic model assessment of insulin resistance (HOMA-IR); low density lipoprotein (LDL); minimal erythemal dose (MED); narrowband ultraviolet B light therapy (nbUVB); parathyroid hormone (PTH); psoralen ultraviolet A light therapy (pUVA); psoriasis area severity index (PASI); ultraviolet A radiation (UVA); ultraviolet B radiation (UVB); quantitative insulin sensitivity check index (QUICKI)

Wavelength/Spectrum-Specific Effects?

The potentially different effects of nbUVB, compared to sun exposure advice, on LDL-cholesterol levels could indicate wavelength-specific or spectrum-related differences in the metabolic effects of UVR from varying sources (i.e. sunlamps versus sunlight). It should also be noted that there was variation in the health status of participants that received nbUVB (mainly individuals with psoriasis[22,23,27]) compared to those administered sun exposure advice (high BMI but otherwise healthy individuals[39,41]). Furthermore, advice for increased sun exposure was sometimes accompanied by other lifestyle advice (e.g. dietary advice to reduce fat intake[39]) and could be confounded by increases in physical activity resulting from more time spent outdoors seeking sun exposure.[39,41] However, these findings are aligned with our pre-clinical studies, in which sun lamps that emitted a spectrum of radiation similar to sunlight reduced blood LDL-cholesterol in mice fed a high fat diet, with this effect not observed in mice exposed to lamps that mainly emitted UVB.[9] They also highlight the capacity for different mediators, which might be produced in response to exposure to specific wavelengths of light, to modulate metabolism through absorption by alternative chromophores and activation of signalling pathways in the skin and eyes.[42] Even within the visible spectrum of light, distinct wavelengths may have different individual capacities to modulate metabolic dysfunction, as demonstrated recently in pre-clinical studies, in which green light (peaking at 520 nm) increased weight gain, signs of glucose intolerance, and hepatic steatosis in mice fed a high fat diet (compared to red or blue light).[43] Our findings also emphasise the importance of measuring personalised levels of sun exposure in intervention studies assessing the effects of UVR administered as part of a phototherapy or advice to increase sun exposure.

Treatment Length and Longitudinal Analyses

Most studies compared the post- to the pre-intervention levels of metabolic and inflammation measures. In one study in adults with psoriasis, PASI scores (measured after 12 weeks) improved before the beneficial effects of nbUVB on circulating adipokines were observed (after 24 weeks of nbUVB).[25] Other studies report significant reductions in circulating pro-inflammatory mediators (e.g. CRP) after ~12 weeks of nbUVB therapy.[23,27,28] These findings suggest that dermal (and systemic) inflammation may drive metabolic dysfunction, and more longitudinal studies that consider the effects of UVR exposure over time are needed. In individuals with psoriasis, longer exposure to nbUVB might be necessary to have benefits on metabolic dysfunction. Alternatively, other observations suggest that having MetS reduces the anti-psoriatic and-inflammatory effects of nbUVB.[19] With new reports that psoriasis severity correlates with blood HbA_{1c} levels,[44] and the likely multi-directional and interacting effects of skin inflammation, chronic systemic inflammation and metabolic dysfunction,[2,3] it will be important to identify how to reduce metabolic dysfunction in individuals with psoriasis. This might include approaches that combine current therapies (including nbUVB, pUVA, biologics) with lifestyle approaches that promote weight loss[21] and improve metabolic function.

Designing Control Groups

Many of the intervention studies reviewed here did not include a control group. Indeed, careful consideration is needed to determine whether it is logistically possible, and ethically correct to randomise individuals into placebo control groups, especially when recruiting participants who need treatment (e.g. for psoriasis flare). In some circumstances, it may not be ethically appropriate to include blinded placebo treatments, because patients who need treatment should be allowed access, and are unlikely to consent to their involvement in a study where there is a risk that they will be placed in a placebo control group. Without evidence for metabolic benefit, there may also be concerns around increasing skin cancer risk for individuals administered UVR who otherwise do not need it. Blinding participants using a plastic covering to block UVR[4] is possible, but difficult to achieve within logistical and space constraints of dermatology clinics and could be noticed by participants (thus removing blinding). Alternatively, a 'placebo' visible light therapy could be used; however, blue light (within the visible spectrum) may have beneficial effects on related outcomes (specifically blood pressure and endothelial function),[45] and other visible light wavelengths may have unexpected effects (as described above for green light[43]), and so may not be suitable for placebo controls. Other studies have used sunscreens to block the effects of UVR,[40] however, it may be difficult to ensure participant compliance for consistent sunscreen application. In studies examining the effects of sun exposure, different types of advice can be 'administered', and for placebo controls, be based on already accepted sun exposure norms, as done in the Sun Exposure and Vitamin D Supplementation study.[46] These should be combined with personalised measurement of sun exposure (e.g. through dosimeters and sun diaries) for accurate determination of adherence to sun exposure advice within treatment and placebo groups.

Limitations of the Identified Studies

As summarised in Table 1, there are a number of limitations in the studies identified in this review. Of importance is the general lack of data reported on the effects of UVR on adiposity and markers of glucose metabolism, which were often inconsistently measured across studies, with data not always shown. Other limitations include a lack of control/placebo groups in many studies, which as discussed above

Table 5. Intervention studies reporting the effects of sun exposure on adiposity and markers of metabolic dysfunction.

Publication Location	Treatment, dose and length (if recorded)	Population and skin type^ (if recorded)	Effects of sun exposure advice on adiposity outcomes*	Effects of sun exposure advice on metabolic outcomes*	Effects of sun exposure advice on other outcomes*
Osmancevic *et al.* 2009[37] Gran Canarias, Norway (health retreat)	'Climate therapy' with a strict schedule of increasing daily levels of sun exposure **(a)**, mean total dose of UVB=166 SED Length: 15 days	N = 20 (14F:6M, mean BMI = 26.6) Adults (mean=47 y) Severe psoriasis Skin type = all type II-III	No change in BMI	Reduced HbA_{1c} Non-significantly reduced glucose No change in heart rate, total cholesterol, lipoprotein(a), triglyceride Reduced LDL:HDL-cholesterol and apolipoprotein B, Increased HDL-cholesterol, apolipoprotein A-I	Reduced PASI score, diastolic blood pressure and vitamin B_{12} Increased 25(OH)D, erythrocyte haemoglobin, erythrocyte folate, homocysteine, urate No change in calcium, folic acid, creatinine, haematocrit, CRP, micro-CRP
Al-Daghri *et al.* 2012[38] Saudi Arabia	Increased sun exposure advice and intake of vitamin D through dietary sources**(b)** Length: 12 months**(c)**	N = 59 (28F:31M, mean BMI = 29.2) Adults (mean = 39 y) Overweight and obesity Skin type not reported	No change in BMI, waist/hip circumference	Reduced MetS prevalence No change in glucose, blood pressure, cholesterol (LDL-, total) Increased HDL-cholesterol Reduced prevalence with high triglyceride	Increased 25(OH)D No change in blood pressure
Al-Daghri *et al.* 2014[39] Saudi Arabia	Increased sun exposure advice, dietary advice to reduce fat and increase fibre intake, and increase physical activity levels**(d)** Length: 6 months	N = 150 (113F:37M, mean BMI = 32.2) Adults (mean = 45 y) Overweight and obesity Skin type not reported	No change in BMI	'Normalised' fasting glucose in individuals with pre-diabetes Increased fasting glucose in non-diabetic individuals Reduced triglycerides, LDL-HDL- and total-cholesterol Increased prevalence of hypertension	Increased 25(OH)D Increased calcium and albumin
Mianowska *et al.* 2016[40] Canary Islands, Tenerife (sun holiday)	Increased sun exposure**(e)** (Uncontrolled, with UVA&UVB-absorbing sunscreen, or with UVB-absorbing sunscreen) Length: 7 days	N = 22 (uncontrolled, BMI not stated) N = 15 (UVA & UVB sunscreen) N = 18 (UVB sunscreen) (21F:34M) Adults (mean = 35 y) Volunteers Skin type = >90% type II-III	†	Reduced fructosamine with sunscreen-protected sun exposure compared to those with uncontrolled sun exposure No change to non-fasting glucose	Skin erythema observed in all individuals with uncontrolled sun exposure, but not other treatments

Publication Location	Treatment, dose and length (if recorded)	Population and skin type^ (if recorded)	Effects of sun exposure advice on adiposity outcomes*	Effects of sun exposure advice on metabolic outcomes*	Effects of sun exposure advice on other outcomes*
Patwardhan *et al.* 2017[41] Pune, Western India	Sun exposure advice (20 min, mid-day**(f)**); or Vitamin D_3 (1,000 IU/d); or Control Length: 6 months	N = 32 (sun exposure advice, mean BMI = 25.3) N = 37 (vitamin D) N = 39 (control) (0F:108M) Adults (mean = 48 y) Vitamin D-deficient, healthy Skin type not reported		Reduced cholesterol (total, HDL-, LDL-), triglyceride	Increased sun exposure (in that treatment) Increased 25(OH)D (in sun exposure and vitamin D_3 treatments)

^Skin type refers to the Fitzpatrick system for scoring skin type from type I (lightest skin, most susceptible to burn with sun exposure) to type VI (darkest skin, least susceptible to burn with sun exposure). *Aside from PASI scores, adiposity/metabolic outcomes/disease prevalence, data refers to metabolites and proteins measured in blood; unless otherwise stated data compares baseline with study end. †Blank fields mean these parameters were not measured in the study rather than there were no significant findings.

25-hydroxyvitamin D (25(OH)D); body mass index (BMI); C-reactive protein (CRP); female:male ratio (F:M); glycated haemoglobin (HbA_{1c}); high density lipoprotein (HDL); low density lipoprotein (LDL); metabolic syndrome (MetS); psoriasis area severity index (PASI); standard erythemal dose (SED)

(a) The patients followed a strict exposure schedule on the first day of the study, exposing first the front side of the body for 30 min, the back side for 30 min, followed by 15 min exposure on each side in the period from about 11:00 to 13:00 local time. They were allowed to stay outside after lunch, with sunscreen applied (SPF25) to the whole body. For the remaining days, the patients were advised to gradually increase the hours of exposure per day, and limit to use sunscreen to locations easily burned.

(b) Advice was for subjects to regularly expose themselves to sunlight (twice a week for 5-30 min before 10 AM, after 3 PM) and increase intake of vitamin D-rich foods (cod liver oil, salmon, tuna, cow liver, dairy products, and vitamin D–fortified foods) through weekly SMS reminders.

(c) Sun exposure and activity levels recorded (in a diary) but not reported.

(d) Advice was for subjects to increase sun exposure, reduce fat intake to <30% of caloric intake and increase fibre intake to 15 g/1000 kCal (with further dietary guidelines as per the Diabetes Prevention Program) and complete 30 min of moderate activity (walking, 5 times a week), through weekly SMS reminders.

(e) Participants had 6 h of sun exposure between 9 AM and 5 PM dressed in two-piece bathing costume (women) or trunks (men).

(f) Participants in the sun exposure arm were advised to have 20 min sunlight exposure to forearms and face between 11 am and 3 pm over and above their current exposure; individuals were advised to go outdoors for a 20 min stroll on work premises or nearby; sun exposure was recorded throughout questionnaire.

may be difficult to do, both ethically and logistically, particularly for those administering phototherapy in clinical settings. Many of the studies had only a small number (often fewer than 30) of participants receiving the UVR intervention, which likely meant that these were underpowered when the effect size was small and/or when outcomes were highly variable. There was also significant variability between studies in the length of treatment (which was sometimes not stated), the wavelength(s) of UVR or doses (or time in the sun) administered, making meta-analyses impractical. Few studies stratified data for BMI/diagnosis of MetS[19] and other important variables, such as skin type and sex. Further, better-powered studies with placebo/control groups are needed that directly measure sun exposure and consider modulating factors such as BMI/diagnosis of MetS, skin type and sex.

In conclusion, we summarised the effects that treatments involving exposure to UVR (through phototherapies or sun exposure advice) have on markers of metabolic dysfunction and adiposity. We identified some possible effects of UVR on circulating concentrations of LDL-cholesterol and blood markers of systemic inflammation. Few studies reported outcomes related to glucose metabolism, most were small in participant size, and compared findings at baseline to endpoint. Therefore, larger more comprehensive studies are needed, including control groups, which assess a range of markers of glucose metabolism and adiposity at multiple time-points. More studies are needed that measure personalised levels of sun exposure (and other lifestyle modifiers) and consider the influence of other factors such as skin type, sex and diagnosis of metabolic disease. Better understanding the impact that exposure to UVR has on metabolic health may lead to the development of more personalised and effective preventative strategies and therapies of psoriasis and other diseases characterised by metabolic dysfunction.

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